II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-48 were pending at the time of the Office Action dated December 20, 2004. Claims 1, 3 and 43 have been amended. No new matter is added by the amendments. Claims 1-48 are now pending and presented herein for reconsideration.

B. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The Action rejects claims 1, 3, 22, and 43 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out the subject matter which Applicant regards as the invention. In particular, the Action asserts that: (1) the meaning of the term "capable of" cannot be ascertained in claims 1, 3 and 43, (2) the meaning of "small molecule" cannot be ascertained in claim 22, and (3) the meaning of "synthetic molecule" cannot be ascertained in claim 22.

(1) The term "capable of"

The Action rejects claims 1, 3 and 43 under 35 U.S.C. § 112, second paragraph on the grounds that the term "capable of" is unclear. In response, Applicants note that the recited term has been amended or deleted in claims 1, 3, and 43 in order to advance the prosecution of the case and because the amendments do not narrow the scope of the claims. Specifically, the term "capable of" as is it used in the claims is inherent in the limitations recited in the original claims as understood by persons having ordinary skill in the art. Thus Applicants do not disclaim any subject matter through the amendment. It is believed that the rejection is moot in light of the amendments.

(2) The term "small molecule"

The Action rejects claim 22 as indefinite under 35 U.S.C. § 112, second paragraph, on the grounds that the term "small molecule" is unclear. Applicants respectfully traverse this rejection. The term "small molecule" has a well established meaning in the art. A skilled researcher would understand that, in the context of the instant specification and claims, the term "small molecule" describes a low molecular weight molecule that is not based on repeating monomeric units. In support of this, Applicants provide the Declaration of Karl E. Griswold, a graduate student in the field of protein engineering. Mr. Griswold notes that the term "small molecule" describes a low molecular weight molecule that is not based on repeating monomeric units, and that this definition is accepted and well known in the art. The Declaration also provides the results of a search in PubMed, a database of relevant scientific literature, that reveals 788 references in which the words "small molecule" appear in the title alone (Appendix A). This evidences that skilled researchers understand the meaning of the term "small molecule," and thus that the term is fully definite.

(3) The term "synthetic molecule"

The Action rejects claim 22 as indefinite under 35 U.S.C. § 112, second paragraph, on the grounds that the term "synthetic molecule" is unclear. Applicants respectfully traverse this rejection. The term "synthetic molecule" has a well established meaning in the art. A skilled researcher would understand that, in the context of the instant specification and claims, the term "synthetic molecule" describes a molecule made through the actions of chemicals or biochemicals, as opposed to a molecule that is isolated from the natural world. In support of this, Applicants provide the Declaration of Karl E. Griswold, a graduate student in the field of protein engineering. Mr. Griswold states that the term "synthetic molecule" is known in the art to

describe a molecule made through the actions of chemicals or biochemicals, as opposed to a molecule that is isolated from the natural world. The Declaration also provides the relevant definition of the term "synthetic" from the online version of the Merriam-Webster online dictionary (http://www.m-w.com/dictionary.htm), given as "produced artificially" (Appendix B). This evidences that those skilled in the art understand the meaning of the term "synthetic molecule" and thus that the use of the term is not indefinite.

In view of the foregoing it is respectfully submitted that the claims are fully definite and removal of the rejection is thus requested.

C. Rejections Under 35 U.S.C. §102

The Action rejects claims 1, 4-9, 13-15, 17-24 and 34-35 under 35 U.S.C. §102(e) as being anticipated by Hultgren *et al.* (US Patent No. 6,001,823), and rejects claims 1-41 and 43-48 under 35 U.S.C. §102(b) as anticipated by Iverson *et al.* (WO 98/49286). Applicants respectfully traverse as set forth below.

1) The Action rejects claims 1, 4-9, 13-15, 17-24 and 34-35 under 35 U.S.C. §102(e) as anticipated by Hultgren *et al.* (US Patent No. 6,001,823). Applicants respectfully traverse as the cited reference does not teach the claim limitations. Current claim 1, upon which each of the remaining rejected claims depends, reads as follows:

> 1. (Currently amended) A method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding polypeptide having specific affinity for a target ligand comprising the steps of:
> (a) providing a Gram negative bacterium comprising an inner and an outer membrane and a periplasm, said bacterium expressing a nucleic acid sequence encoding a candidate binding polypeptide, wherein the candidate binding polypeptide is exposed within the periplasm of said bacterium;
> (b) contacting the bacterium with a labeled ligand under conditions wherein the labeled ligand contacts the binding polypeptide; and

(c) selecting said bacterium based on the presence of said labeled ligand bound to said candidate binding polypeptide.

The Action has not shown teachings in the cited reference demonstrating either of steps (b) or (c), nor a basis for concluding that such steps are suggested by the reference. For example, step (b) requires contacting the bacterium from step (a) with a labeled ligand. Hultgren *et al.* does not teach this step. Rather, Hultgren involves first contacting an **isolate of proteins with a labeled ligand**, and second, contacting a **bacteria with an unlabeled ligand**, but not contacting a **bacteria with a labeled ligand** as recited in step (b). For example, the assay described in column 14 that uses a "fluorescence labeled variant" is described in Example 10, column 84 of the Hultgren patent to contact a "purification" of protein with the labeled variant. The cited reference therefore does not teach or suggest contacting a bacterium with the labeled variant either here or elsewhere. Furthermore, the assay described in columns 10 and 11 of the Hultgren patent recites contacting bacteria with a "substance." This substance is defined in columns 6 and 7 as a compound with the effect of "prevention, inhibition, or enhancement of binding between the pilus subunits and a periplasmic molecular chaperone." The Hultgren patent does not teach or suggest that the substance used to contact the bacterium is a labeled ligand. Because the reference teaches first contacting an **isolate of proteins** with a labeled ligand, and second, contacting a bacterium with an **unlabeled ligand**, but not contacting a bacterium with a **labeled** ligand, there is no teaching in the cited reference of step (b) of claim 1, and the claim cannot be anticipated.

Similarly, step (c) of claim 1 entails "selecting said bacterium based on the presence of said labeled ligand bound to said candidate binding polypeptide." Hultgren *et al.* also does not teach this step. Rather, Hultgren teaches a method for selecting a **substance** based on **comparing growth rates** within a sample of bacteria, not a method for selecting a **bacterium**

from a sample based on the **presence of labeled ligand within the bacterium** as recited in step (c). For example, the assays described in columns 10-12 of the Hultgren patent recite methods for "testing a candidate substance... by determination of the growth rate of the bacteria." The cited reference teaches the determination of growth rate as follows:

> By counting of colonies on solid agar plates striped with the bacteria, by counting bacterial density in liquid growth media (OD_{600} determination), by measuring fluorescence of substances such as NAD(P)H, ATP, or amino acids, which are contained in the bacterial cells only, or by any other convenient detection system known to the person skilled in the art.

The foregoing does not teach detection of a labeled ligand as the substances detected are native to the bacterial cells themselves. Specifically, the reference teaches measuring fluorescence of substances that are unlabeled and "contained in the bacterial cells." Labeled ligands are neither contained in bacterial cells nor are bacterial cells labeled under Hultgren. Therefore, the reference fails to teach the determination of growth rate based on the presence of a labeled ligand. Additionally, Hultgren teaches measuring fluorescence or using "any other convenient detection system known to the person skilled in the art" for "the determination of growth rate" and "identifying the substance as potentially therapeutic," and does not teach measuring fluorescence or the using any convenient detection systems for **selecting a bacterium** based on the presence of a labeled ligand as recited in step (c). Furthermore, as is discussed in the preceding paragraph, since Hultgren *et al.* fails to teach contacting bacteria with a labeled ligand, the reference necessarily fails to teach selection of a bacteria "based on the presence of said labeled ligand within the periplasm." Because no teaching in Hultgren *et al.* has shown for selecting a bacterium based on the presence of a labeled ligand, there is no teaching in the cited reference of step (c) of claim 1, and the claim cannot be anticipated.

Applicants further note that the cited reference does not suggest the claimed method as Hultgren is directed towards obtaining a therapeutic substance, not obtaining a bacterium

encoding a binding protein as recited in claim 1. For example, the Hultgren patent teaches the identification of a potentially therapeutic substance, and does not teach that the selection of a bacterium will identify whether a substance is potentially therapeutic. Therefore, the Hultgren patent would not suggest or motivate one with skill in the art to select a bacterium as recited in step (c). Similarly, Hultgren teaches that the identification of a substance as potentially therapeutic is accomplished by determination of growth rate, which would not be accomplished by contacting a bacterium with a labeled ligand. Therefore, the Hultgren patent does not suggest or motivate a person with skill in the art to contact a bacterium with a labeled ligand as recited in step (b), or to select a bacterium based on the presence of a labeled ligand as recited in step (c). Because no teaching in Hultgren *et. al.* teaches, suggests or motivates a person with skill in the art to practice step (b) or step (c) of claim 1, the claims cannot be anticipated or rendered obvious by the cited reference.

2) The Action rejects claims 1-41 and 43-48 under 35 U.S.C. §102(b) as allegedly anticipated by Iverson *et al.* (WO 98/49286). Applicants respectfully traverse as the cited reference does not teach the claimed method.

The Action has not alleged teachings of the cited reference showing any of steps (a) – (c) nor a basis for concluding that such steps can be found in the reference. For example, step (a) of claim 1 entails providing a Gram negative bacterium expressing a binding polypeptide that it is exposed within the periplasm. The Action alleges that Iverson teaches **cell-surface expression**, but not expressing a binding polypeptide that it is **exposed within the periplasm**. Similarly, step (b) entails contacting the bacterium with a labeled ligand under conditions wherein the labeled ligand contacts the binding polypeptide that is **exposed within the periplasm**. Again, no teaching of Iverson has been alleged indicating contacting a gram negative bacterium with a

labeled ligand under conditions wherein the labeled ligand contacts a binding polypeptide that is exposed within the periplasm. Rather, Iverson teaches contacting a gram negative bacterium with a labeled ligand under conditions wherein the labeled ligand contacts the binding polypeptide that is **expressed on the cell surface** (see, e.g., page 47 lines 26-32 and page 48 lines 1-3 of Iverson patent).

Finally, step (c) of claim 1 entails "selecting said bacterium based on the presence of said labeled ligand bound to said candidate binding protein." The Action, however, alleges identification of **cell surface-bound** ligands, but not "based on the presence of said labeled ligand bound to said candidate binding protein" wherein "the candidate binding polypeptide is exposed within the periplasm of said bacterium."

Therefore, the Action does not show all steps of the claimed invention can be found in the prior art. Removal of the rejection is thus respectfully requested.

D. Rejection Under 35 U.S.C. §103(a)

The Action rejects claims 1-48 under 35 U.S.C. §103 as allegedly being obvious over Iverson *et al.* (WO 98/49286) in view of Staudenmaier *et al.* (Journal of Bacteriology, May 1989, p. 2626-2633). Applicants respectfully traverse.

Establishment of a prima facie case of obviousness requires that the prior art teach or suggest all claim limitations, provide a motivation or suggestion to combine the references to arrive at the invention, and provide a reasonable expectation of success in making the combination. *See In re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991), *see also*, M.P.E.P. § 2142. These requirements are not met in the current case. Staudenmaier *et al.* is stated in the Action to teach that FecC and FecD are hydrophobic polypeptides that are localized

in the cytoplasmic membrane. However, Staudenmaier *et al.* does not remedy the deficiencies described herein above with respect to Iverson *et. al.* and claim 1.

Staudenmaier is directed towards characterizing a transport mechanism in a bacterium, not towards obtaining a bacterium wherein the candidate binding polypeptide is exposed within the periplasm as recited in claim 1. For example, Staudenmaier teaches the identification of a periplasmic-binding-protein-dependent transport mechanism, and does not teach that selecting a bacterium will identify a transport mechanism as periplasmic-binding-protein-dependent. The cited reference fails to teach the step of "selecting said bacterium" at all. Therefore, Staudenmaier would not suggest or motivate one with skill in the art to select a bacterium as recited in step (c). Similarly, Staudenmaier teaches that the identification of a transport mechanism as periplasmic-binding-protein dependent is accomplished by determining "the number, structural characteristics, and locations of the FecBCDE proteins" (see Abstract), which would not be accomplished by using FecC or FecD as an inner membrane lipoprotein exposing a binding protein. Therefore, Staudenmaier would not suggest or motivate one with skill in the art to use FecC or FecD to expose a binding polypeptide within the periplasm as recited in step (a). Still further, there could not have been an expectation of success to arrive at the invention with out a teaching of all elements of the claimed invention, let alone the motivation to do so. As such, the cited prior art cannot render the claimed invention obvious.

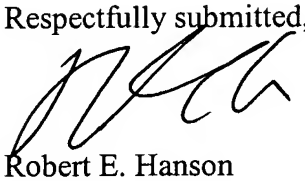
Removal of the rejection under 35 U.S.C. §103 is thus respectfully requested.

E. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the

undersigned (512)536-3085 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: March 4, 2005